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2019 update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis

Antonis Fanouriakis[1], Myrto Kostopoulou[2], Kim Cheema[3], Hans-Joachim Anders[4], Martin Aringer[5], Ingeborg Bajema[6], John Boletis[7], Eleni Frangou[8,27], Frederic Houssiau[9], Jane Hollis[10], Alexandre Karras[11], Francesca Marchiori[12], Stephen D. Marks[13], Gabriella Moroni[14], Marta Mosca[15], Ioannis Parodis[16], Manuel Praga[17], Matthias Schneider[18], Josef S. Smolen[19], Vladimir Tesar[20], Maria Trachana[21], Ronald van Vollenhoven[22], Alexandre Voskuyl[23], Y.K. Onno Teng[24], Bernadette van Leeuw[25], George Bertsias[26*], David Jayne[3*], Dimitrios T. Boumpas[1,27,28*]

[1] *Rheumatology and Clinical Immunology Unit, "Attikon" University Hospital and Department of Rheumatology, "Asklepieion" General Hospital, Athens, Greece*

[2] *Department of Nephrology, "G. Gennimatas" General Hospital, Athens, Greece*

[3] *Department of Medicine, Cambridge, Cambridge, United Kingdom*

[4] *Division of Nephrology, Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany*

[5] *Division of Rheumatology, Department of Medicine III, University Medical Center & Faculty of Medicine Carl Gustav Carus at the TU Dresden, Dresden, Germany*

[6] *Department of Pathology, Leiden University Medical Center, Leiden, Netherlands*

[7] *Nephrology Department and Renal Transplantation Unit, "Laikon" Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece*

[8] *Department of Nephrology, Limassol General Hospital, Limassol, Cyprus*

[9] *Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium*

[10] *Lupus Nurse Specialist, Addenbrooke's Hospital, Cambridge, United Kingdom*

[11] *Department of Nephrology, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France*

[12] *Lupus Europe, Rome, Italy*

[13] *University College London Great Ormond Street Institute of Child Health, NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom*

[14] *Nephrology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

[15] *Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*

[16] *Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Rheumatology, Karolinska University Hospital, Stockholm, Sweden*

[17] *Nephrology Department, Research Institute Hospital Universitario 12 de Octubre (i+12), Department of Medicine, Complutense University, Madrid, Spain*

[18] *Department of Rheumatology & Hiller Research Unit Rheumatology, UKD, Heinrich-Heine University, Du□sseldorf, Germany*

[19] *Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria*

[20] *Department of Nephrology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic*

[21] *Pediatric Immunology and Rheumatology Referral Center, First Pediatric Clinic, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[22] *Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Center, Amsterdam, Netherlands*

[23] *Rheumatology and Immunology Center, location VU Medical Center, Amsterdam University Medical Center, Amsterdam, Netherlands*

[24] *Centre of expertise for Lupus-, Vasculitis- and Complement-mediated Systemic autoimmune diseases, Department of Internal Medicine – section Nephrology, Leiden University Medical Center, Leiden, Netherlands*

[25] *Lupus Europe, Essex, United Kingdom*

[26] *Rheumatology, Clinical Immunology and Allergy, University Hospital of Heraklion, Greece*

[27] *Laboratory of Autoimmunity and Inflammation, Biomedical Research Foundation of the Academy of Athens, Athens, Greece*

[28] *Joint Academic Rheumatology Program, Medical School, National and Kapodestrian University of Athens, Athens, Greece and Medical School, University of Cyprus, Nicosia, Cyprus*

* *These authors contributed equally to this work*

Corresponding author: Dimitrios Boumpas, MD, FACP

National and Kapodestrian University of Athens

12462 Athens, Greece, Tel.: (+30) 210 5831990 - E-mail: boumpasd@uoc.gr

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Abstract

To update the 2012 EULAR/ERA-EDTA recommendations for the management of lupus nephritis (LN), we followed the EULAR standardised operating procedures. The changes include recommendations for treatment targets, use of glucocorticoids and calcineurin inhibitors (CNI), and management of end-stage-kidney-disease (ESKD). The target of therapy is complete response (proteinuria <0.5-0.7gr/24h with [near-]normal glomerular filtration rate) by 12 months, but this can be extended in patients with baseline nephrotic-range proteinuria. Hydroxychloroquine is recommended with regular ophthalmological monitoring. In active proliferative LN, initial (induction) treatment with mycophenolate mofetil (MMF 2-3g/day, or mycophenolic acid at equivalent dose) or low-dose intravenous cyclophosphamide (CY; 500mg x6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3-0.5mg/kg/day) is recommended. MMF/CNI (especially tacrolimus) combination and high-dose CY are alternatives, for patients with nephrotic-range proteinuria and adverse prognostic factors. Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no or low-dose (<7.5 mg/day) glucocorticoids. The choice of agent depends on the initial regimen and plans for pregnancy. In non-responding disease, switch of induction regimens or rituximab are recommended. In pure membranous LN with nephrotic-range proteinuria or proteinuria >1g/24h despite renin-angiotensin-aldosterone blockade, MMF in combination with glucocorticoids is preferred. Assessment for kidney and extra-renal disease activity, and management of comorbidities is lifelong with repeat kidney biopsy in cases of incomplete response or nephritic flares. In ESKD, transplantation is the preferred kidney replacement option with immunosuppression guided by transplant protocols and/or extra-renal manifestations. Treatment of LN in children follows the same principles as adult disease.

Keywords: Systemic lupus erythematosus, treatment, lupus nephritis

Introduction

Up to 40% of systemic lupus erythematosus (SLE) patients develop kidney disease, which represents a major cause of morbidity.[1–3] In 2012, the European League Against Rheumatism-European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) developed joint recommendations for lupus nephritis (LN),[4] involving a panel of rheumatologists, nephrologists, renal pathologists and paediatricians. Since then, new evidence has emerged, which includes the use of calcineurin inhibitors (CNI) and "multitarget" therapy, disease monitoring and treatment targets. We therefore sought to update the recommendations for the management of LN.

Methods

Following approval by the EULAR and ERA/EDTA Executive Committees, the convenors (DB, DJ) invited a multidisciplinary panel of 11 rheumatologists, 11 nephrologists, 1 nephropathologist, 1 paediatric rheumatologist, 1 paediatric nephrologist, 1 allied health professional and 2 patient representatives. The EULAR standardised operating procedures[5] were followed and the Appraisal of Guidelines Research and Evaluation instrument was employed.[6] Delphi-based methodology led to 15 questions for systematic literature review (SLR), which was undertaken by three fellows (AF, MK, KC) (**Table 1**). PubMed was searched using specific index terms and retrieved items were evaluated based on the title, abstract and/or full text. Since this is an update of the 2012 recommendations, we considered all English-language publications between 01/2012 and 12/2018. The total number of articles included are shown in **Table 1**.

Table 1. Questions to be addressed by the systematic literature review and final number of articles included.

Diagnosis and classification of lupus nephritis	**Total number of articles included**
1. What is the prognostic significance of kidney biopsy findings?	33
2. Risk stratification of patients of lupus nephritis by incorporating demographic, clinical and histological data	64
Pharmacologic treatment of lupus nephritis	
3. What is the evidence for the benefits and harms of hydroxychloroquine in lupus nephritis?	16
4. 'Induction' therapies in lupus nephritis (including dosage of glucocorticoids, and use of calcineurin inhibitors)	127
5. 'Maintenance' therapies in lupus nephritis (including dosage of glucocorticoids, and use of calcineurin inhibitors)	
Monitoring and therapeutic targets	

6. How should lupus nephritis be monitored?	85
7. What is the goal of treatment in lupus nephritis?	18
8. Duration of immunosuppressive treatment in lupus nephritis	16
Refractory lupus nephritis	
9. What is the definition of refractory lupus nephritis?	13
10. How should refractory/flaring lupus nephritis be treated?	36
Special topics in lupus nephritis	
11. Management of lupus nephritis during pregnancy and lactation	17
12. Management of antiphospholipid syndrome nephropathy	18
Chronic kidney disease in lupus nephritis	
13. Management of end stage renal disease in lupus nephritis	42
14. Renal transplantation in patients with lupus nephritis	44
Comorbidities and adjunct therapy in lupus nephritis	
15. Comorbidities in lupus nephritis (cardiovascular, infections)	49

The number of included studies refers to studies published after January 2012. The final level of evidence and grading of recommendations considered the total body of evidence, including the 2012 recommendations for lupus nephritis.

The results of the literature search were summarized, distributed to all members, presented and discussed upon, during the meeting of the panel in May 2019. The previous recommendations[4] were re-appraised and revised accordingly. The final level of evidence (LoE; scale: 1 to 4) and grading of recommendations (GoR; scale: A [highest] to D [lowest]), according to the Oxford Centre for Evidence Based Medicine definitions,[7] (**Supplementary Table 1**) considered the total body of evidence. Each member of the panel was then asked to rate their level of agreement (LoA) for each statement on a 0–10 rating scale (10 being full agreement), based on both the research evidence presented and their own clinical expertise. For the final voting, Task Force members had the "opportunity" to express their potential disagreement for a particular statement, however omission of statements with less consensus was not considered necessary. The methods and results of the SLR will be published separately.

Results

The overarching principles and specific recommendations, with the respective LoE, GoR and LoA, are listed in **Table 2**.

Table 1. Overarching principles and recommendations for the management of patients with lupus nephritis. The level of evidence (LoE), grading of recommendations (GoR) and final level of agreement (LoA) are shown in bold for each recommendation.

Overarching principles		
Kidney involvement in SLE, a major cause of morbidity and mortality that leads to high medical and societal costs, is best managed by interdisciplinary care with shared patient-physician decisions.		
Vigilance for symptoms and signs suggestive of kidney involvement, histological assessment by nephropathologists and input from specialized centres ensure optimal outcomes.		
Goals of treatment include patient survival, long-term preservation of kidney function, prevention of disease flares, prevention of organ damage, management of comorbidities and improvement in disease-related quality of life.		
Management of active phases of lupus nephritis includes an initial period of intense immunosuppressive therapy to control disease activity, followed by a longer period of usually less intensive therapy to consolidate response and prevent relapses.		
Recommendation/Statement	**LoE/GoR**	**LoA, mean (SD)**
1. Investigation of the patient with suspected lupus nephritis		
1.1 Kidney biopsy should be considered when there is evidence of kidney involvement, especially in the presence of persistent proteinuria ≥0.5 g/24hr (or urine protein-creatinine ratio [UPCR] ≥500 mg/g in morning first void urine), and/or an unexplained decrease in glomerular filtration rate.	**2b/B** **2b/C**	**9.84 (0.54)**
1.2 Kidney biopsy remains indispensable and its diagnostic and prognostic value cannot be substituted by other clinical or laboratory variables.	**2b/B**	**9.96 (0.20)**
2. Pathological assessment of kidney biopsy		

2.1 The use of the International Society of Nephrology/Renal Pathology Society 2003 classification system is recommended, with additional assessment of activity and chronicity indices, as well as of thrombotic and vascular lesions associated with antiphospholipid antibodies/syndrome.	**2a/B** **1b/A** **2b/C**	**9.56 (0.94)**
3. Indications for immunosuppressive treatment		
3.1 Immunosuppressive agents, administered in combination with glucocorticoids, are recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis.	**1a/A**	**9.96 (0.20)**
3.2 In pure class V nephritis, glucocorticoids and immunosuppression are recommended in cases of nephrotic-range proteinuria, or when UPCR exceeds 1000 mg/g despite the optimal use of renin-angiotensin-aldosterone system blockers	**2b/B** **5/D**	**9.04 (1.80)**
4. Treatment of adult lupus nephritis ***Goals of treatment***		
4.1 Treatment aims for optimization (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months, 50% by 6 months, and a UPCR target below 500–700 mg/g by 12 months (*complete clinical response*)	**2b/D** **2a/B** **2a/B**	**9.60 (0.63)**
4.2 Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to reach *complete clinical response*; in such cases, prompt switches of therapy are not necessary if proteinuria is improving.	**2a/C**	**9.68 (0.68)**

Initial treatment		
4.3 For patients with class III or IV (±V) lupus nephritis, mycophenolate mofetil (MMF; target dose: 2 to 3 g/day, or mycophenolic acid sodium [MPA] at equivalent dose) or low-dose intravenous (IV) cyclophosphamide (CY) (500 mg every two weeks for a total of 6 doses) in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.	**1a/A** **1a/A**	**9.84 (0.37)**
4.4 Combination of mycophenolate mofetil (MMF; target dose: 1 to 2 g/day, or mycophenolic acid sodium [MPA] at equivalent dose) with a calcineurin inhibitor (especially tacrolimus) is an alternative, particularly in patients with nephrotic-range proteinuria.	**1a/B**	**9.32 (0.93)**
4.5 Patients at high risk for kidney failure (reduced glomerular filtration rate, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in **4.3-4.4,** but high-dose IV CY (0.5–0.75 g/m^2 monthly for 6 months) can also be considered	**2b/B** **1a/B**	**8.88 (1.56)**
4.6 To reduce cumulative glucocorticoid dose, the use of IV pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5mg/day by 3 to 6 months.	**2b/C**	**9.48 (0.90)**
4.7 In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose), in combination with pulse IV methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months) is recommended as initial treatment due to best efficacy/toxicity ratio.	**2a/B** **2b/C**	**9.28 (0.96)**

4.8 Alternative options for class V nephritis include IV CY, or calcineurin inhibitors (especially tacrolimus) in monotherapy or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria.	**2b/B** **2b/B** **1b/B**	**9.28 (0.92)**
4.9 Hydroxychloroquine (HCQ) should be co-administered, at a dose not to exceed 5 mg/kg/day and adjusted for the glomerular filtration rate.	**2a/B** **3b/C**	**9.28 (1.40)**
Subsequent treatment		
4.10 If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day) – especially if it was used as initial treatment – or azathioprine (AZA; 2 mg/kg/day) – preferred if pregnancy is contemplated-, in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity.	**1a/A** **1a/A**	**9.80 (0.49)**
4.11 Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in *complete clinical response*. HCQ should be continued long-term.	**2b/C**	**9.40 (0.75)**
4.12 Continuation, switching to or addition of calcineurin inhibitors (especially tacrolimus) can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks.	**2b/B**	**9.28 (1.15)**
Non-responding/Refractory disease		
4.13 In case of failure to achieve the treatment goals, thorough evaluation of the possible causes is recommended, including assessment of adherence to treatment and therapeutic drug monitoring.	**5/D**	**9.84 (0.46)**
4.14 For active non-responding/refractory disease, treatment may be switched to one of the alternative initial therapies mentioned *above*,	**2b/B–C**	**9.64 (0.62)**

or rituximab (1000 mg on days 0 and 14) may be given	**2b/C**	
5. Adjunct treatment		
5.1 Angiotensin converting enzyme-inhibitors or angiotensin receptor blockers are recommended for all patients with UPCR >500 mg/g or arterial hypertension.	**5/D**	**9.84 (0.37)**
5.2 Statins are recommended on the basis of lipid levels and estimated 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation or other validated tools.	**5/D**	**9.52 (0.75)**
5.3 Bone protection (calcium/vitamin D supplementation and/or anti-resorptive agents) and immunizations with non-live vaccines may reduce treatment- and disease-related comorbidities and are recommended.	**5/D**	**9.68 (0.61)**
5.4 If antiphospholipid antibodies (defined as in the international consensus statement for definite antiphospholipid syndrome classification criteria) are positive, and based on antiphospholipid antibody profile, acetyl-salicylic acid (80-100 mg/day) may be used after balancing benefits and bleeding risk.	**2a/C**	**9.28 (1.25)**
5.5 Anticoagulant treatment should be considered in cases of nephrotic syndrome with serum albumin <20 g/L.	**5/D**	**9.76 (0.43)**
5.6 Belimumab may be considered as add-on treatment, to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease the risk for extra-renal flares.	**2a/C**	**8.48 (1.92)**
6. Monitoring and prognosis of lupus nephritis		
6.1 Visits should be scheduled every 2–4 weeks during the first 2–4 months after diagnosis or flare, and subsequently, according to response to treatment. Monitoring for renal, extra-renal disease activity and co-morbidities is life-long.	**5/D**	**9.40 (0.69)**
6.2 At each visit, body weight, blood pressure (including out-of-office measures), estimated glomerular filtration rate, serum albumin, proteinuria (UPCR or 24-hour urine collection), urine red cell count or sediment, and complete blood cell	**2b/B**	**9.64 (0.69)**

count should be evaluated when nephritis is active and less frequently if stable. Serum C3/C4 and anti-dsDNA antibody levels are monitored periodically.	**2b/C**	
6.3 Repeat kidney biopsy should be considered in selected cases, such as worsening of kidney variables, non-responsiveness to immunosuppressive or biologic treatment (as defined *above*); or at relapse, to demonstrate possible histologic class transition or change in chronicity and activity indices; to provide prognostic information; and detect other pathologies.	**2b/B**	**9.84 (0.37)**
7. Management of end-stage kidney disease in lupus nephritis		
7.1 All methods of kidney replacement treatment can be used in SLE patients.	**2b/B**	**9.96 (0.20)**
7.2 Immunosuppression in end-stage kidney disease on dialysis should be guided by extra-renal manifestations.	**2b/C**	**9.76 (0.59)**
7.3 Transplantation may be preferred over other kidney replacement options and should be considered when extra-renal lupus is clinically (and ideally, serologically) inactive for at least 6 months; outcomes are better with living donor and pre-emptive transplantation.	**2b/C**	**9.84 (0.37)**
7.4 Antiphospholipid antibodies should be measured during transplant preparation, because they are associated with an increased risk of vascular events in the transplanted kidney.	**2b/C**	**9.48 (1.10)**
8. Antiphospholipid syndrome and lupus nephritis		
8.1 In patients with antiphospholipid syndrome-associated nephropathy, antiplatelet/anticoagulant treatment can be considered, in addition to HCQ.	**2b/C**	**9.68 (0.55)**

9. Lupus nephritis and pregnancy		
9.1 Pregnancy may be planned in stable patients with inactive lupus nephritis. Optimally, UPCR should be below 500 mg/g for the preceding 6 months, with glomerular filtration rate >50 ml/min.	**1b/A** **2b/C**	**9.56 (0.80)**
9.2 Compatible medications such as HCQ, prednisone, AZA and/or calcineurin inhibitors (especially tacrolimus) should be continued at safe dosages throughout pregnancy and lactation.	**1b/B** **3b/C** for all	**9.76 (0.51)**
9.3 MMF/MPA should be withdrawn at least 3–6 months before conception is planned, to ensure that an alternative immunosuppressive agent does not lead to a relapse.	**5/D**	**9.29 (0.93)**
9.4 During pregnancy, acetylsalicylic acid is recommended to reduce the risk of pre-eclampsia.	**2b/C**	**9.64 (0.62)**
9.5 Patients should be assessed at least every 4 weeks, preferably by a multidisciplinary team including an obstetrician with expertise in the disease.	**5/D**	**9.56 (0.80)**
9.6 Flares of lupus nephritis during pregnancy can be treated with acceptable medications stated above and pulses of IV-MP, depending on flare severity.	**3b/C**	**9.56 (1.39)**
10. Management of paediatric patients		
10.1 Lupus nephritis in children is more common at presentation and more severe with increased damage accrual; the diagnosis, management and monitoring are similar to that of adults.	**3b/C**	**9.68 (0.68)**
10.2 A coordinated transition program to adult specialists is essential to ensure adherence to therapy and optimization of long-term outcomes.	**5/D**	**9.84 (0.37)**

Overarching principles

Despite an improved prognosis over the last decades,[8] LN poses therapeutic challenges and is linked to increased morbidity, mortality and healthcare costs. The nature of the disease (involvement of the kidneys in the context of a systemic autoimmune disease) mandates a multidisciplinary approach by rheumatologists and nephrologists, following histologic confirmation and assessment of LN by a nephropathologist. In this regard, management or periodic evaluation of these patients in centres with expertise is recommended. Decision making requires that the patient is adequately informed about the nature and natural course of the disease and the therapeutic options.

Recommendations

1. *Investigation of the patient with suspected lupus nephritis*

SLE patients with any sign of kidney involvement (glomerular haematuria and/or cellular casts, proteinuria >0.5 g/24h [or spot urine protein-to-creatinine ratio (UPCR) >500 mg/g], unexplained decrease in glomerular filtration rate [GFR]) are candidates for kidney biopsy. Mild clinical presentations (e.g. sub-nephrotic proteinuria) can nonetheless be associated with active histological lesions.[9–11] In a review of kidney biopsies performed during 1970-2016, earlier use of biopsy based on urinary abnormalities, as done from 2001-2016, was associated with improved outcomes, despite similar rates of severe histology.[12] The benefits of histologic evaluation should be balanced against increased bleeding risk in selected patients such as those receiving anticoagulation. All patients with SLE, especially those with suspected kidney involvement, should be tested for antiphospholipid antibodies (aPL), since renal manifestations of antiphospholipid syndrome, such as thrombotic microangiopathy (TMA), may carry prognostic implications. Testing for anti-dsDNA and anti-C1q (whenever available) autoantibodies should be considered in patients with suspected LN, along with complement levels (C3 and C4).[13]

2. *Pathologic assessment of kidney biopsy*

The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification still represents the gold standard for assessment of kidney biopsy in LN (**Supplementary Table 2**).[14] TMA lesions, albeit not pathognomonic, should raise suspicion of antiphospholipid syndrome nephropathy and thus, prompt aPL (re-)testing. Although TMA has been reported in up to 25% of LN biopsies,[15][16] its prognostic implications remain unclear.[17][18] Tubulointerstitial lesions, such as interstitial fibrosis and tubular atrophy, are associated with poor outcome.[19–21] A revision of the 2003 ISN/RPS classification has recently been proposed and awaits endorsement.[22]

3. *Indications of immunosuppressive treatment in lupus nephritis*

Immunosuppressive treatment is recommended in active class III or IV LN, with or without co-existing histological chronicity. For pure class V LN, the recommendation for immunosuppression pertains to patients with nephrotic-range proteinuria, which is associated with worse prognosis, in addition to cases with proteinuria >1 g/24h despite optimal use of renin-angiotensin-aldosterone system blockers for a reasonable time period (e.g. at least 3 months). Class II LN usually does not need specific immunosuppressive therapy, but may be prone to histologic transformation to more aggressive disease on repeat biopsy. The presence of significant proteinuria should prompt histologic reassessment for detection of proliferative changes that may have been overlooked.

4. *Treatment of adult lupus nephritis*

Goals of treatment

Compared to the previous recommendations, the goals of treatment were further defined according to time since treatment initiation. Post-hoc analyses from the MAINTAIN and Euro-Lupus Nephritis trials suggest that proteinuria at 12 months represents the best single predictor for long-term renal outcome [i.e. risk for end-stage kidney disease (ESKD) or doubling of serum creatinine after 10 years].[23–27] Accordingly, therapy should aim for proteinuria <0.5-0.7 g/24h by 12 months (*complete clinical response*), although up to 50% of patients not reaching this milestone may still have stable long-term kidney function.[25,28] Evidence of improvement in proteinuria (with GFR normalization/stabilization) should be noted by 3 months,[29,30] and at least 50% reduction in proteinuria (*partial clinical response*) by 6 months. For patients with nephrotic-range proteinuria at baseline, the aforementioned time frames may be extended by 6-12 months, due to slower proteinuria recovery.[31] Thus, consideration of decreasing proteinuria can avoid premature treatment changes. Since SLE is a systemic disease, immunosuppressive therapy should also target remission or low disease activity from extra-renal domains.[32]

Initial treatment

In **class III-IV LN**, an updated Cochrane systematic review suggested similar efficacy of mycophenolate mofetil/mycophenolate acid (MMF/MPA) compared with cyclophosphamide (CY),[33] with possible ethnic/racial differences, i.e. MMF potentially being more efficacious in African-Americans.[34] The 10-year Euro-Lupus Nephritis Trial data showed equal efficacy of low-dose *versus* high-dose CY,[24] and the low-dose regimen has been used in non-European populations.[35–38] Consequently, both MMF/MPA and low-dose CY are recommended as *first-line* options for initial (*induction*) treatment. The recommended target dose of MMF is now changed to 2-3 g/day (MPA 1.44-2.16 g/day), based on evidence that therapeutic drug dosage may range between 1 and 3 g/day. Dose may be adjusted according to tolerance/adverse effects, efficacy, and

trough MPA blood levels. High-dose IV CY (0.5-0.75 gr/m^2 monthly for 6 months) can be considered in patients with adverse clinical (nephritic urine sediment and impaired renal function with GFR between 25 and 80 ml/min) or histological (crescents or necrosis in > 25% of glomeruli) prognostic factors.[39]

The realization of the adverse effects of long-term glucocorticoid treatment, together with emerging evidence that following initial pulse IV methylprednisolone, lower starting dose of glucocorticoids (≤0.5 mg/kg/day) may as efficacious as higher dose,[40–42] led the Task Force to recommend that total IV methylprednisolone dose may range from 500-2500 mg (allowing flexible dosing depending on disease severity), starting oral prednisone dose may be 0.3-0.5 mg/kg/day, reducing to ≤7.5mg/day by 3 to 6 months.

Focus has been placed on the use of calcineurin inhibitors [CNI, tacrolimus (TAC) and cyclosporine A (CsA)], either as a monotherapy or in combination with MMF/MPA.[43–46] A randomized controlled trial (RCT) in 362 Chinese patients found the combination of TAC/MMF to be superior to CY in the short-term. In a phase 2 RCT, a cyclosporine analogue, voclosporin when combined with MMF was associated with a higher frequency of complete response at 6 months as compared to MMF alone, although more side-effects and deaths occurred in the former group.[42] A number of meta-analyses suggest that CNI (alone or as part of multitarget regimen) may have favorable efficacy/toxicity ratio in LN,[47] and thus, in a new statement (4.4), the combination of MMF with a CNI (especially TAC) is included as therapeutic option, particularly in cases with nephrotic-range proteinuria. Until more data in non-Asian populations and studies with longer follow-up and on renal outcomes such as prevention of kidney insufficiency/failure are available, CNI and the "multitarget" regimen cannot be universally recommended as first-line treatment. Additionally, nephrotoxicity and other side-effects of CNI use should be considered when opting for a CNI-based regimen.

In pure **class V LN**, no high-quality evidence has emerged over the last 7 years. MMF/MPA is recommended as first-choice at the same doses as in class III/IV disease. CY and CNI (especially TAC), the latter as monotherapy or combined with MMF, are alternative options.[43,48] Similar to class III/IV LN, rituximab (RTX) is reserved for non-responders in class V LN (*see below*), although a recent RCT in idiopathic membranous nephropathy, which demonstrated short-term superiority over CsA, may justify a modification once similar data emerge in LN.[49]

Hydroxychloroquine (HCQ) is recommended for all patients with LN, in the absence of contraindications. HCQ use is linked to reduced risk of kidney flares, ESKD and death.[50–54] In light of emerging data regarding ocular toxicity with more sensitive screening techniques, and in accordance to a revised statement by the American Academy of Ophthalmology, daily HCQ dose should not exceed 5 mg/kg actual body weight and should be continued indefinitely with regular ophthalmologic screening (after 5 years on HCQ and yearly thereafter, or yearly from baseline in the presence of risk factors).[32,55] Dose adjustments (50% reduction) and yearly eye monitoring from onset are recommended for patients with GFR <30 ml/min.

Subsequent treatment

MMF/MPA and AZA remain the drugs of choice for subsequent immunosuppressive treatment, following adequate response during the initial phase. The two regimens did not differ in terms of kidney flares in the 10-year follow-up of the MAINTAIN trial,[24] in contrast to the ALMS maintenance study which showed superiority of MMF.[55] Based on evidence showing increased relapses when MMF/MPA is followed by AZA,[56,57] we recommend MMF/MPA induction to be followed by MMF/MPA maintenance. CY induction can be followed by either MMF/MPA or AZA; the latter agent is preferred if pregnancy is contemplated or the higher cost of MMF is an issue. CNI can be used in class V LN at the lowest effective dose, since chronic use of these agents may increase the risk of kidney side-effects.

Most renal flares occur within the first 5-6 years following treatment initiation.[24,58–61] Therefore, for most patients it is recommended not to discontinue immunosuppression prior to that time. Therapy de-escalation should be contemplated in patients who have attained sustained *complete renal response* and GC should be tapered first. Gradual immunosuppressive drug tapering is recommended prior to complete withdrawal. Both longer duration of treatment and longer duration of remission were associated with reduced risks of kidney flares in patients who discontinued immunosuppressive therapy after 6 years of treatment.[52,62] To this end, duration of immunosuppressive therapy should be individualized according to the timing and magnitude of response, duration of flare-free maintenance, extra-renal SLE activity and patient preferences.[63]

Non-responding/Refractory disease

Failure to achieve the treatment goals described above raises the possibility for non-responding or refractory disease. In this context, proteinuria kinetics are important as a decreasing proteinuria – to a level not yet meeting these targets – could justify further waiting prior to therapy switch, especially in patients with nephrotic-range proteinuria at baseline, provided that kidney function is stable. Thorough assessment, including adherence to treatment with measurement of drug levels, where available, is warranted prior to declaring non-responding/refractory disease (the role of repeat kidney biopsy is discussed *below*).

All first-line therapies, including MMF/MPA (2-3 g/day),[64] CY and CNI (especially TAC) as monotherapy or “multitarget” therapy,[65–68] are recommended in non-responding disease. B-cell depleting therapies such as RTX, albeit off-label, are also indicated either as mono- or as add-on therapy to MMF/MPA or CY;[69–73] complete depletion of circulating B-cells predicted clinical remission at 76 weeks.[74] This has recently been supported by a successful trial of obinutuzumab.[75] Following a response to RTX, relapses are not uncommon, but occur after a variable length of time.[76,77] Repeat dose can be considered to prevent or treat a relapse. Although belimumab is not formally indicated for treating LN, *post-hoc* analyses from RCTs and observational studies suggest that, when added to standard-of-care (including MMF), it may gradually reduce proteinuria and the risk for kidney flares.[78–82] Importantly, positive results from the phase 3 RCT of belimumab as an add-on therapy in LN have been released,[83] and the results of this study are awaited. The combination of RTX and belimumab has recently been used in refractory disease.[84] High dose intravenous

immunoglobulin (2g/kg) could be considered when there are contraindications to increasing glucocorticoids or immunosuppressive drugs, such as infection,[85] while plasma exchange is rarely indicated.

5. *Adjunct treatment in patients with lupus nephritis*

Renin-angiotensin-aldosterone system blockade is recommended (in non-pregnant patients) due to its antiproteinuric and antihypertensive effects; judicious use and dose titration is warranted in cases of impaired renal function. Hypertension should be controlled to values below 130/80 mm Hg (Tselios 2014). General kidney-protective measures (e.g. avoidance of nonsteroidal anti-inflammatory drugs) cannot be over-emphasized. Vaccination status should be reviewed and patients be vaccinated accordingly with non-live vaccines.[86] Vaccination against influenza and *Streptococcus pneumoniae* are strongly recommended; regarding vaccination against herpes zoster, existing data suggest an acceptable safety profile of the live attenuated vaccine (available in most countries) in lupus patients. The decision should be individualized, taking into account patient age and net state of immunosuppression. Patients under less intensive immunosuppression may be more appropriate for vaccination.

Statin therapy should be considered on the basis of lipid levels and presence of other cardiovascular risk factors; calculation of the 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation, QRisk3, or other validated score is recommended to aid this decision, taking into account that such scores may underestimate the actual risk especially in young SLE patients.[32,87] Primary prevention of thrombosis with low-dose aspirin is recommended in the presence of high-risk aPL profile, balancing thrombotic versus bleeding risk.[88] Bone protection and prevention of osteoporosis should follow non-pharmacologic (exercise uptake, maintenance of normal body mass index) as well as pharmacologic measures, according to fracture risk.

6. *Monitoring and prognosis of lupus nephritis*

Patients should be assessed periodically in centres with experienced clinicians interpreting urine microscopy, serology and histology.[89] Kinetics of proteinuria and serum creatinine within the first 6-12 months are more sensitive than haematuria in predicting long-term prognosis. Quantification of proteinuria can be done by means of a spot UPCR, as its correlation with a 24h-urine protein collection is high in most studies (albeit lower when urine protein is <1000 mg/24h).[90–92] 24h-urine protein may be preferred prior to therapeutic decisions. Urinalysis should be included at each visit; re-appearance of glomerular haematuria or cellular casts can be a predictor of impending kidney flare.[93] Serum C3/C4 and anti-dsDNA should be monitored; although a rise in anti-dsDNA titres has been associated with an forthcoming flare, the specificity is modest.[94–96] Anti-C1q antibodies have the highest correlation with active LN and may also predict relapse.[97,98]

Repeat kidney biopsy can be considered in cases of non-responsiveness to immunosuppressive treatment, to differentiate between ongoing activity and irreversible damage, or in cases of relapse. Following a LN flare, histological transition is found in 40-76%, typically from class V to III-IV forms.[93,99] *Per protocol* repeat biopsies following immunosuppressive treatment frequently show a discordance between clinical and histologic response, as 30% of complete responders have ongoing histologic activity.[100] The value of protocol re-biopsy to determine the need for continuous treatment was examined in a prospective study of 36 LN patients who were in complete remission for 12 months following 3 years of immunosuppressive therapy. Ongoing histologic activity was strongly predictive of a subsequent kidney flare when reducing immunosuppression.[101]

7. Management of end-stage-kidney disease in lupus nephritis

Recent studies suggest that the risk for ESKD in LN has decreased to less than 10% at 15 years.[8,12] Still, some patients will progress to irreversible kidney injury, which carries increased risks of morbidity and mortality.[102–104]. Once on kidney replacement therapy, the disease usually follows a quiescent course and flares (renal and extra-renal) are less frequent but still can occur. Among kidney replacement modalities, haemodialysis and continuous peritoneal dialysis are accompanied by similar patient survival rates in comparative retrospective studies.[105,106] By contrast, kidney transplantation is associated with higher 10-year patient survival rates;[107,108] data from the United States Renal Data System showed 70% reduced mortality among LN-ESKD patients who underwent transplantation as compared to non-transplanted counterparts.[109] The updated statement now emphasizes that "*transplantation may be preferred over other kidney replacement options and should be considered when extra-renal lupus is clinically (and ideally, serologically) inactive for at least 6 months*". Currently, only a small fraction of patients undergo pre-emptive transplantation, although this strategy has the most favourable outcome (10-year patient survival rates 94%,versus 76% and 42%, for peritoneal dialysis and haemodialysis, respectively).[103,110] Transplantation should not be delayed and can be safely performed in the presence of isolated serologic activity. Recurrent LN in the transplanted kidney is rarely clinically significant. Transplanted LN patients are at increased risk of opportunistic infections due to their previous drug exposures.

8. Antiphospholipid syndrome and lupus nephritis

Antiphospholipid syndrome-associated nephropathy represents a rare -yet distinct- type of aPL-induced vascular nephropathy. Although considered a hallmark of antiphospholipid syndrome-associated nephropathy, TMA, is not pathognomonic, because similar lesions are found in thrombotic thrombocytopenic purpura/haemolytic uraemia syndrome, malignant hypertension or complement-mediated TMA.[111,112] There are no controlled studies to guide the treatment of antiphospholipid syndrome-associated nephropathy. Antiplatelet agents or anticoagulants (if criteria for antiphospholipid syndrome are fulfilled) are

recommended, in addition to HCQ. Renin-angiotensin-aldosterone system blockade may delay disease progression.[113]

9. *Lupus nephritis and pregnancy*

The 2017 EULAR recommendations for the management of family planning in SLE and antiphospholipid syndrome fully cover the issue of pregnancy, including assisted reproduction, in the context of LN.[114] In the absence of new evidence, the statements of the 2012 recommendations for pregnancy LN were kept unchanged. UPCR should be controlled (ideally, to <500 mg/g) without the use of renin-angiotensin-aldosterone system inhibitors, which are contraindicated in the first trimester due to teratogenicity. Compatible drugs include glucocorticoids, AZA and CNI, and HCQ, which should be continued at safe dosages throughout pregnancy and lactation.[115,116] Withdrawal of MMF for longer period, e.g. six months before attempts for conception, offers time to assess the tolerability and efficacy of an alternative immunosuppressive.[117] Severe flares during pregnancy - not responding to drugs with an acceptable safety profile - merit multidisciplinary specialist referral; occasionally, termination of pregnancy and/or use of embryotoxic drugs may be considered after balancing the risk/benefit ratio.

10. *Management of paediatric lupus nephritis*

Renal involvement is more common in childhood compared to adult-onset SLE, often as a presenting manifestation, while renal flares are observed in more than 50% of patients.[118,119] Since the 2012 EULAR/ERA-EDTA recommendations, American and European groups of experts in paediatric SLE and LN have published recommendations for the management of child-hood onset LN; both are largely based on data extrapolation from the studies in adults.[120,121] Notwithstanding differences between children and adults, the respective statements from the 2012 recommendations remained unchanged; diagnosis, treatment (paediatric doses of drugs, **Supplementary Table 3**) and monitoring should follow the same principles as in adult disease. For children in adolescence, a transition program is recommended to ensure adherence and optimal outcomes.

Table 3. Research agenda in lupus nephritis

Diagnosis
Clinical presentation, histopathologic features, response to treatments, prognostic factors and genetic background (e.g. *APOL1*) in various ethnicities
Revision of the ISN/RPS classification criteria (under way)
Atypical lupus nephritis: Podocytopathies and pauci-immune lupus nephritis, other forms

Approach to non-lupus (or antinuclear antibody negative) full-house glomerulonephritis Validated definition of kidney flares
Existing therapies and disease monitoring CNI efficacy in non-Asian patients B-cell targeting therapies (eg. belimumab, combination of rituximab and belimumab, obinutuzumab) and cytokine inhibitors in lupus nephritis Imaging for kidney fibrosis Duration and withdrawal of therapy Damage accrual in long-term disease Protocolized repeat biopsies: value of early (*versus* late) repeat biopsy Non-immune mechanisms in progression of lupus nephritis, such as hypertension, obesity, dyslipidaemia Impact of patient education programs Role of eculizumab in antiphospholipid syndrome associated-nephropathy
Pathophysiology and Biomarkers Risk stratification of subgroups based on molecular signatures or other biomarkers Explore non-invasive means to classify the types of lupus nephritis and activity status (urine cells, omics, etc) Renal progenitor cells and their proliferation in lupus nephritis Kidney repair in lupus nephritis Biomarkers for liquid biopsy
Lupus Nephritis Trial Design Risk stratification of subgroups based on molecular signatures or biomarkers Innovative trial designs Optimization of 'standard-of-care' (background) treatments Better definition of clinical trial endpoints

Discussion

Recent insights in LN necessitated an update of the EULAR-ERA/EDTA recommendations, which were developed by a large group of physicians from different specialties and nurses caring for LN, with input from patients, and complement the updated recommendations for SLE.[32] Inclusion of all involved medical disciplines is an advantage and accords to the multidisciplinary care that these patients need. These recommendations intend to inform rheumatologists, nephrologists, patients, national professional societies, hospital officials, social security agencies and regulators about the treatment of LN based on most recent evidence, to ensure optimal outcomes with existing therapies. In addition to the quality of evidence for risks and benefits, considerations were also given to the availability and costs of treatments.

A challenging issue is the absence of licenced medications for LN, in spite of high-quality evidence supporting the use of existing drugs. Again, in these recommendations, MMF and low-dose IV CY are recommended as drugs of first choice based upon their better toxicity profile, while allowing room for the use of high-dose IV CY for selected patients with aggressive disease, especially if gonadal toxicity is not a consideration. CNI, especially TAC, in combination with glucocorticoids and MMF in the so called "*multitarget*" therapy, have been included. The absence of robust evidence on CNI in non-Asian populations and their potential for renal toxicity with chronic use has led the committee to adopt a more cautious attitude, recommending them for patients with nephrotic-range proteinuria or not responding to initial therapy. Glucocorticoid usage, in view of their contribution to damage in SLE, received special attention in these recommendations with the committee recommending the use of pulse glucocorticoids, followed by lower doses of daily glucocorticoids to decrease cumulative dose. Glucocorticoid reduction is receiving increased attention in recent years, being used as an outcome measure in SLE trials.[122]

The development of new classification criteria for SLE with increased weighting for kidney disease will facilitate the inclusion of more patients in LN trials.[123] New drugs in development for LN, including novel CNI, B-cell inhibiting and depleting agents, kinase inhibitors, inhibitors of co-stimulation, inhibitors of complement activation, in combination with improved trial designs, may provide additional agents in the near future.

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